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Mo. MI2003 A 000820

It is certified that the annexed copy is compliant with the original documents as filed with the above mentioned patent application, the data of which are reported in the enclosed filing certificate.

Rome, April 27, 2004

The Manager
Giampietro Carlotto

Seal of the Patent Office

TO THE MINISTRY OF INDUSTRY COMMERCE AND ARTISANSHIP FORM A
Central Patent Office - ROME
Application for industrial invention, late filing, unavailable to the public
A. Applicant(S)
1) Denomination CHEMI SPA
Residence CINISELLO BALSAMO (MI) Identification Code
2) Denomination
Residence Identification Code
B. REPRESENTATIVE OF APPLICANT AT CENTRAL PATENT OFFICE
Surname, name Pistolesi Roberto et al Fiscal Code
Agent's name and Office **DRAGOTTI & ASSOCIATI SRL**
Street **Galleria San Babila** No. **4/C** Town **Milano** Postal Code **20122** Prov. **MI**
C. ELECTIVE DOMICILE
Street No. Town Postal Code Prov.
D. TITLE Suggested class (sec/cl/scl) group/undergroup
POLYMORPHOUS FORMS OF ROSIGLITAZIONE MALEATE
Unavailable to the public Yes No If there is a petition Reg. No.
E. DESIGNATED INVENTORS Surname and Name Surname and Name
1) TURCHETTA Stefano 3) AROMATARIO Valentina
2) MASSARDO Pietro 4)
F. PRIORITY

Nation	Type	Number	Date	Encl.		Resolution of saving clause	
1)					S/R	Date	Reg. No.
2)							

H. SPECIAL REMARKS

ENCLOSED DOCUMENTS

Doc. 1) 2	REP.	No. page 11	abstract with first drawing description and claims (1 ex. compulsory)	Resolution of saving clause Date	Reg. No.
Doc. 2) 2	REP.	No. 06	drawing or photo (1 ex. compulsory)		
Doc. 3) 1	REP.		Substitutive Declaration		
Doc. 4) 0	REP.		designation of inventor		
Doc. 5) 0	REP.		priority document with translation into Italian		
Doc. 6) 0	REP.		authorisation or assignment deed		
Doc. 7) 0			applicant's full name		
8) Payment certificate € 188,51				compulsory	

Executed on 18/04/2003 The Applicant(s) on behalf of
Continues YES/NO no CHEMI SPA
Certified copy of the above deed is asked YES/NO Yes

DISTRICT OFFICE INDUSTRY COMMERCE AND ARTISANSHIP OF **MILAN** Code **15**
FILING RECORD Application No. MI2003A 000820 Reg. A
In the year 2003 on the day 18 of the month of April the above indicated applicant(s) submitted to me, the undersigned, said application consisting of No. 00 additional sheets for the grant of the patent under reference.
VARIOUS REMARKS OF THE RECORDING OFFICER

THE FILING PERSON OFFICE STAMP RECORDING OFFICER
Illegible signature M. Cortonesi

Abstract of utility model with the first design, description and claims
Application No. MI2003A 000820 Reg. A filing date 18/04/2003
Patent No. granted date

D. TITLE

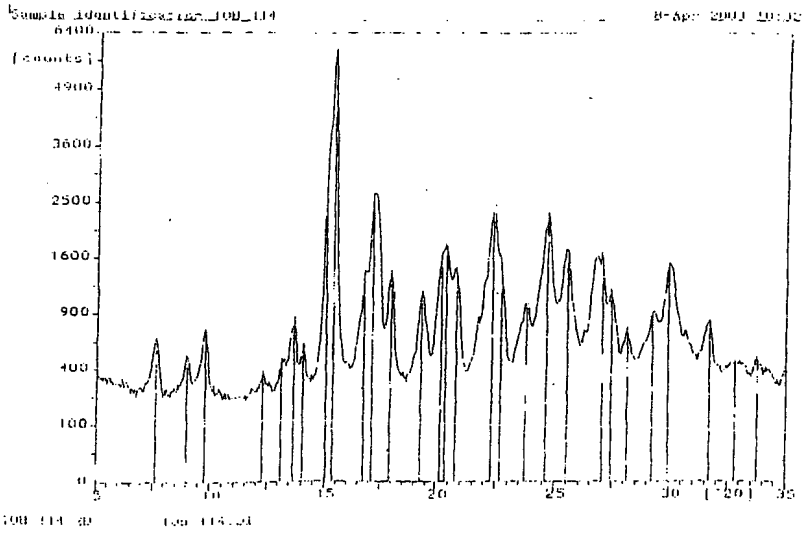
POLYMORPHOUS FORMS OF ROSIGLITAZIONE MALEATE

L. ABSTRACT

Two new polymorphous crystalline forms of rosiglitazone maleate, termed respectively form I and II, and the methods for selectively obtaining each form are described and characterized. Rosiglitazone maleate may be obtained in the form of the single polymorph I by blending an approximately equimolar mixture of rosiglitazone base and maleic acid in a series of solvents and mixtures thereof which comprises isopropanol, acetone, ethyl acetate, isopropyl acetate, followed by cooling of the mixture to ambient temperature; the form II may on the other hand be obtained by means of treatment of the approximately equimolar mixture of rosiglitazone base and maleic acid in water under reflux, followed by cooling of the mixture to ambient temperature

M. DESIGN

FIGURE 4



Description of the industrial invention in the name of CHEMI SPA

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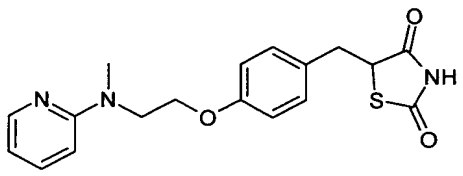
FIELD OF THE INVENTION

The present invention relates to the synthesis and characterization of two polymorphous forms of rosiglitazone maleate.

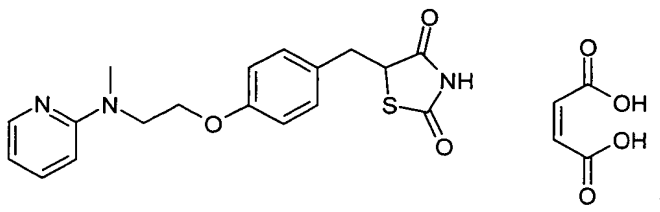
STATE OF THE ART

Rosiglitazone is a molecule of thiazolidinedione structure which forms part of the class of antidiabetics. Its structure formula is given below.



US 5,002,953 describes for the first time the compound and its use as an antihyperglycaemic. In that patent all its pharmaceutically acceptable salts are also claimed.

US 5,741,803 instead specifically describes the maleate of rosiglitazone, shown below, stating that among the possible salts, the maleate exhibits particularly favourable characteristics of stability and solubility in water.



In that patent, two examples of the preparation of the salt in question are given. In the first example the

compound is prepared by hot dissolution of the rosiglitazone base mixed with maleic acid, and slow precipitation of the salt derived therefrom. After treatment of the suspension at 0-5°C for several hours, a product is isolated which, when dried under vacuum at 50°C provides a product having a melting point (m.p.) of 120-121°C. The ^{1}H-NMR of the product is provided in which a wide band between 2 and 5 ppm is found which the applicant attributes to the residual water contained in the solvent (not otherwise specified). In the second example the maleate of rosiglitazone is treated, in ethanol, with an equivalent of maleic acid, while hot, until dissolution of the solid is obtained, the mixture is decoloured with carbon and the product is precipitated by cooling to 0-5°C, then the product is filtered and desiccated, having at the end of the treatments a m.p. of 119-119.5°C.

US 6,515,132 relates to a method for the synthesis of rosiglitazone maleate, in which the step of formation of the maleate of rosiglitazone is carried out in acetone.

DESCRIPTION OF THE INVENTION

It is known in fact that many organic compounds and their salts may exist in the form of a plurality of different crystalline structures, which exhibit different physical properties and may exhibit differences also from the biological point of view.

In the course of experiments on crystallization of the maleate of rosiglitazone it was surprisingly found that this salt, under specific conditions, crystallizes in three different polymorphic crystalline pure forms, that have not been described before.

Obtaining pure crystalline forms is extremely useful, both because through these a precise characterization

of the chemical-physical properties is possible, and because these characteristics may prove more favourable from a pharmacological point of view.

The subject of the present patent application is therefore a new polymorphous form II of rosiglitazone maleate, and also the methods necessary for the crystallization of polymorphous forms I and II.

DETAILED DESCRIPTION OF THE INVENTION

Tests on the synthesis of rosiglitazone maleate carried out starting from equimolar amounts of rosiglitazone base and maleic acid surprisingly led to the identification and characterization of two polymorphous crystalline forms of the aforesaid salt.

In particular, it was found that the maleate of rosiglitazone exists in two polymorphous crystalline modifications, which may be easily distinguished both by means of DSC, and IR, and also X-ray diffraction.

Rosiglitazone maleate exists in a polymorphous form I, which with the DSC exhibits an endothermic peak with maximum at 119°C (Figure 1) and in a polymorphous form II, which with the DSC exhibits an endothermic peak with maximum at 121°C (Figure 2). The DSCs were carried out with a Perkin Elmer DSC7 Differential Scanning Calorimeter.

The two forms have a powder diffraction spectrum to X-rays characterized by the following principal absorptions (Radiation Cu Kα, Generator voltage 40 kV, Divergence Slit 1°, Receiving slit 0.2 mm, scan mode step start angle 5,000, End angle 35,000, time per step 2,000 sec):

FORM I (figure 3)

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.570	11.6687	2.4
8.580	10.2972	5.2
9.355	9.4458	8.1
14.005	6.3183	6.4
15.125	5.8529	41.4
16.005	5.5330	100.0
17.160	5.1631	10.0
18.625	4.7601	31.0
20.240	4.3838	6.8
21.000	4.2268	13.9
21.990	4.0387	32.9
22.785	3.8996	12.1
23.585	3.7691	30.0
25.055	3.5512	60.4
26.480	3.3632	18.0
28.425	3.1374	11.9
28.905	3.0863	8.6
30.430	2.9351	8.1
31.395	2.8470	6.7
32.145	2.7823	8.9
33.990	2.6353	9.3

FORM II (figure 4)

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.615	11.5998	7.4
8.985	9.8340	4.8
9.740	9.0733	9.3
13.635	6.4889	11.6
14.015	6.3138	7.1
15.320	5.7788	100.0
17.105	5.1796	43.8
17.910	4.9485	21.8
19.255	4.6058	16.7
20.330	4.3646	27.8
20.765	4.2741	21.7
22.285	3.9859	37.8
23.730	3.7464	14.1
24.610	3.6144	37.7
25.485	3.4922	27.0
27.030	3.2960	24.4
27.440	3.2477	17.0
28.135	3.1690	8.7
29.225	3.0533	12.7
29.905	2.9854	24.1
31.645	2.8251	11.5

The X-ray diffractions were carried out with a Philips PW3710 X-ray Diffractometer.

Form I exhibits with IR characteristic absorptions at the following wavelengths (Figure 5): 1744; 1618; 1262; 1178; 1083; 1070; 997, 823; 778 cm^{-1}.

Form II exhibits with IR the following characteristic absorptions (Figure 6): 1757; 1610; 1162; 1062; 1030; 926; 835; 767 cm^{-1}.

The IR spectra were carried out with a Perkin Elmer 16 PC FT-IR spectrometer.

Rosiglitazone maleate may be obtained in the form of the single polymorph I by blending an approximately equimolar mixture of rosiglitazone base and maleic acid in a series of solvents and mixtures thereof, which comprises isopropanol, acetone, ethyl acetate, isopropyl acetate, THF, by heating the suspension to reflux temperature of the solvent, followed by cooling of the mixture to ambient temperature. In this way a crystalline suspension of the product is obtained which, when filtered, washed and desiccated under vacuum for 12 hours at 45-50°C provides rosiglitazone maleate form I as the single crystalline form, as confirmed by IR, XRD and DSC analyses.

Form II of rosiglitazone maleate, however, may be obtained in a pure form by treatment of the approximately equimolar mixture of rosiglitazone base and maleic acid in water under reflux, followed by cooling of the mixture to ambient temperature. The solid suspended in the mixture may be filtered, washed and desiccated under vacuum for 12 hours at 45-50°C and consists exclusively of crystals of Form II of rosiglitazone maleate.

EXAMPLE 1

Synthesis of Rosiglitazone maleate Form I.

A 250 ml balloon flask equipped with mechanical stirring, coolant and thermometer, is charged with 10 g (28.0 mmoles) of rosiglitazone base, 3.25 g (28.0 mmoles) of maleic acid and 75 ml of isopropanol. The mixture is brought to reflux and maintained for 30'

under such conditions. The mixture is then slowly cooled to ambient temperature and the product is filtered on a Buchner filter, washing twice with 10 ml of isopropanol. The filtered product is then desiccated for 12 hours at 45-50°C. 9.7 g of rosiglitazone maleate Form I (yield 73%) are obtained. The content of residual isopropanol in the product is 0.16% by weight.

EXAMPLE 2

Synthesis of Rosiglitazone maleate Form II.

A 500 ml balloon flask is charged with 20 g (56.0 mmoles) of rosiglitazone base and 6.50 g (56.0 mmoles) of maleic acid. To these solids are added 350 ml of water, and the mixture obtained is brought to reflux for 30'. The mixture is then slowly cooled to ambient temperature and the resultant solid is filtered on a Buchner filter, washing twice with 20 ml of water each time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 19.9 g (yield 75%) and consists of rosiglitazone maleate Form II. The water content of the desiccated product is 0.3%.

EXAMPLE 3

Synthesis of rosiglitazone Form I.

Example 1 is repeated, using isopropyl acetate as solvent in place of the isopropanol. After desiccation, 9.5 g of rosiglitazone maleate Form I (yield 72%) are obtained.